REMARKS

The Office Action mailed July 18, 2001, has been received and its contents carefully noted. Claims 1-6, 9-15, 43, and 44 were rejected and claims 16-42, and 45 were withdrawn from consideration. Claims 1-15, 43, and 44 have been canceled and rewritten as new claims 46-65 to more accurately point out what Applicants regard as their invention. Support may be found in the specification generally. No new statutory matter has been added. Reconsideration is respectfully requested.

Objection of Specification

The Examiner objected to the specification because of the recitation of "us of" twice at page 6, line 13.

Applicants have reviewed the specification, in particular, page 6 and can not find the duplicate recitation of "us of". Enclosed herewith is a copy of page 6 of the specification as originally filed. Applicants respectfully request the Examiner's assistance in pointing out the offending phrase.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-6 and 9-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which Applicant regard as the invention.

Specifically, the Examiner deemed that:

A) the phrases "enabling", "desired sequences", "if necessary, "if present", and "and/or" fail to ascertain the claimed invention with precision;

B) the metes and bounds of "mimics" are indefinite; and

C) claim 10 is indefinite for the recitation of "at least one of the sequences is derived from a sequence …".

Applicants respectfully submit that the claims as amended obviate rejections A and C above. Applicants respectfully submit that the term "mimics" in claim 54 is not indefinite as its scope and meaning is clear to one of skill in the art. Specifically, from the numerous references, patents, and patent applications that disclose peptide mimics and peptide mimetics one of skill in the art would understand that the commonly accepted meaning of a "mimic" or "mimetic" of a peptide refers to a substance that has the essential biological activity of a given peptide. The peptide mimic may be a molecule comprising at least one peptide that mimics elements of the protein secondary structure. A peptide mimic allows the molecular interactions similar to the given peptide. A peptide mimic includes substances that are not peptides but retains the essential biological activity of the given peptide.

As applied in the instant case, the mimics of claim 54, refer to substances that exhibit the biological activity of all or

part of a B cell epitope, all or part of a T cell epitope, or a combination thereof. Therefore, Applicants respectfully submit that the term "mimics" does not render the present claims indefinite and the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Claim Objections

The Examiner objected to claims 7-8 (presented herein as new claims 52 and 53) as being improper multiple dependent claims.

Applicants respectfully point out that in the Preliminary Amendment to Lessen Fees filed with the original application on September 29, 1999, claim 7 was amended to be dependent on claim 2 only, as the phrase "according to claims 1-5" in line 3 was deleted. Claim 8 was dependent on claim 7 only. Applicants respectfully submit that claims 7-8 are not improper multiple dependent claims and should have been examined on the merits. Consequently, the claim objections should be withdrawn and claims 52-53 should be examined on the merits.

Election of Species

Applicants respectfully submit that former claims 16-18 and 45, now new claims 60-62 and 65, respectively, are in fact encompassed in Applicants' elected species. Before responding to the specific art rejections, it is important to note that the

present invention relates to ***a method for the preparation*** of an LPA having free C-terminal groups by the use of an ***achiral*** di-, tri-, or tetra-carboxylic acid so as to provide a construct having a ring structure.

The claims clarify that one of the peptide sequences is derived from *Mycobacterium tuberculosis*. Throughout the specification, Applicants disclose and teach that the presented C- and N-terminal sequences may be different. See, for example, the last paragraph of page 31. One of the peptide sequences may be derived from *Mycobacterium tuberculosis* and the other peptide sequence being OpsC derived from *Borrelia burgdorferi*. The C-terminal presented peptide may be OpsC derived from *Borrelia burgdorferi*, and the N-terminal presented peptide may be a sequence derived from *Mycobacterium tuberculosis*. Thus, Applicants respectfully submit that claims 60-62 and 65 are encompassed in the elected species and should be maintained and examined.

Rejection under 35 U.S.C. § 102(a)/102(b)

The Examiner rejected claims 1-6 as being anticipated under 35 U.S.C. 102(a) by Lange et al. or under 102(b) by Gilon et al. or Mihara et al.

Lange et al. relates to the synthesis and activity of dimeric bradykinin antagonists containing diaminodicarboxylic acid bridge residues. Lange et al. teaches the synthesis of short

peptide chains, including up to three amino acids (H-(D-Phe)-Leu-Arg-resin), on a solid support. The free N-terminal amino group (0.2 mmol) was reacted with 0.08 mmol bis(Fmoc)-2,7-diaminosuberic acid (suberic acid = $HOOC(CH_2)_6COOH$) or bis(Fmoc)-2,9-diaminosebacic acid (sebacic acid = $HOOC(CH_2)_8COOH$) using PyBOP and HOBt for 18 hours. Unreacted resin-bound amino groups were then capped with excess acetic anhydride (p. 291, 1st column "Dimeric Petides 4c and 4d").

The method of Lange et al. is decisively different from the method of the present invention. Specifically, the method of Lange et al. requires the use of a coupling dicarboxylic acid comprising two ***chiral*** centers. The claimed methods of the present invention utilize only ***achiral*** dicarboxylic acids to give optically pure products rather than racemic mixtures. Therefore, Lange et al. do not anticipate the present invention as claimed.

Next, Applicants respectfully submit that Gilon et al. deals with ***backbone*** cyclization as a tool for imposing conformational constraint on peptides. The concept and purpose described in Gilon et al. is clearly different from that of the present invention. Gilon et al. provides a process wherein the peptides are synthesized by solid phase peptide synthesis including N-(omega-amino alkylene) Glycine in position 9 and an Arginine in position 6. The cyclic analogs are formed by cyclizing the amino groups of the mentioned amino acids in position 6 and 9 with

dicarboxylic acids, thus forming lactam rings of 17-22 atoms. These lactam rings are completely different from the products of the present invention and the cyclization of Gilon et al. is ***intra***-molecular as compared to ***inter***-molecular cyclization of the present invention. Inter-molecular cyclization avoids the problems of racemisation and further allows the multiple presentation of ligands. The use of achiral acids to provide inter-molecular cyclization reactions and the benefits thereof are not disclosed or taught in Gilon et al. Therefore, Gilon et al. do not anticipate the present invention as claimed.

Mihara et al. concerns peptides with two α-helix segments anchored on 2,2'-bipyridyl-4,4'-dicarboxylic acid. The peptides are synthesized by solid phase synthesis on Kaiser's oxime resin. After completed assembly of the peptide chain on the synthesis resin the peptide is cleaved off the resin and the free peptide reacted with the anchor, Bpy-(beta-Ala)2 or Sub-(beta-Ala)2 with BOP and HOBt ***in DMSO solution*** (Abstract, line 6-7; p. 1134, column 2, line 21 from below) to give peptides with two α-helix segments anchored together.

The anchoring of two peptide chains by ***solution*** synthesis is completely different from the present invention, which is based on ***solid phase cyclization*** of two peptide chains still attached to the synthesis resin. Coupling of two identical residues, such as amines, alcohols, or phenols with a dicarboxylic acid in solution

is a standard operation in a chemical laboratory but the knowledge of such processes can not be used for ***cyclization of two peptide chains with an achiral dicarboxylic acid to give a macrocyclic ring on a solid support*** which is the case in the present invention. Therefore, Mihara et al. does not anticipate the invention as claimed.

As Lange et al., Gilon et al., and Mihara et al, do not anticipate the present invention as claimed, the rejection under 35 U.S.C. 102(a) and (b) should properly be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-6 and 9-15 under 35 U.S.C. 103(a) as being unpatentable over either Mathiesen (WO 97/422210) and Tomalia et al. in view of any one of Lange et al., Gilon et al., or Mihara et al. Specifically, the Examiner deemed that although Mathiesen and Tomalia et al. do not teach cyclization of the linear OspC peptide, one of ordinary skill in the art would be motivated to cyclize the linear peptide using dicarboxylic acid of Lange et al., Gilon et al., or Mihara et al. of cyclization results in a stable peptide. Applicants respectfully submit that the combination of either Mathiesen et al. or Tomalia et al. with or Lange et al., Gilon et al., or Mihara et al., fail to alleviate the deficiencies in the disclosures of Lange et al., Gilon et al., or Mihara et al. Hence, the combinations cannot render the present

invention as claimed obvious.

The disclosures of the prior art, alone or in combination, do not disclose, teach, or suggest forming a macrocyclic ring system by reacting the N-terminal amino group of two identical peptide chains comprising at least 15 amino acids each and still attached to the synthesis resin with an achiral dicarboxylic acid.

The state of the art of amino acid bridging techniques can be learned from the 1993 report by Alberts et al. (Ref. 17 cited in the present specification) which teaches that bridging with a half equivalent 2,7-bis(Boc-amino) suberic acid coupled to one equivalent of lysine (2Cl-Z-protected) attached to the synthesis resin is slow and takes place over up to 4 days (p. 358, line 14). Thus, ring formation of longer amino acid sequences may be similar or more difficult requiring activation conditions, which could prevent formation of well-defined products with optically active bridging compounds.

Therefore, at the time of the priority of the present invention it would not have been obvious to one of ordinary skill in the art that a macrocyclic ring system could be formed with a reasonable expectation of success by reacting the N-terminal amino group of two identical peptide chains still attached to the synthesis resin and with at least up to 15 amino acids in each chain (LPA-VII), with an achiral dicarboxylic acid. On the

contrary, the slow reactions described with very short chains (1 to 3 amino acids), as cited above, pointed to the opposite. The reasons for this difference is not known but it may be due to the particular amino acids used in the above cited works. In the present invention, achiral dicarboxylic or tricarboxylic acids are used in order to avoid racemization problems which arise where longer or higher coupling activation with the dicarboxyl acid is necessary.

Nowhere in the cited prior art is the use of achiral carboxylic acids taught or suggested in a process for solid phase cyclization. As the cited prior art, alone or in combination, do not result in the present invention as claimed, a *prima facie* case has not been established. As the Examiner has not established a *prima facie* case of obviousness, the rejection under 35 U.S.C. §103(a) should properly be removed.

CONCLUSION

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims and to find this application to be in allowable condition.

If the Examiner believes that a conference would be of value in expediting the prosecution of this application, the Examiner is invited to telephone the undersigned to arrange for such a conference.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By # 43,172 for
Harvey B. Jacobson, Jr.
Reg. No. 20,851

400 Seventh Street, N.W.
Washington, D.C. 20004-2201
(202) 638-6666
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